



## Presentation Abstract

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Title: Enhanced neuroprotection by neurturin (NRTN) in 6-OHDA rats following combined substantia nigral plus striatal delivery of AAV2-NRTN (CERE-120)

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Abstract: AAV2-NRTN is under development as a novel treatment for Parkinson's disease (PD). NRTN, like GDNF, can protect nigrostriatal dopamine neurons from degeneration and thus has potential as a novel therapeutic for PD patients. While early research clearly established the potent bioactive effects of GDNF in 6-OHDA lesioned rats following direct targeting of dopaminergic cell bodies in the substantia nigra (SN), later research argued that targeting the terminal fields of these neurons (the striatum) was both necessary and sufficient, whereas targeting the SN was superfluous and sometimes detrimental. More recently, analyses of autopsy tissue from PD patients treated with CERE-120 indicate that in advanced PD, only limited amounts of NRTN are transported from the targeted striatum to the cell bodies in the SN. Those novel data suggest that to be maximally effective, neurotrophic factors must be delivered to both the terminal fields and cell bodies of PD nigral neurons. As part of a continuing program to develop CERE-120 for PD, we assessed the effectiveness of administering CERE-120 directly to the SN of 6-OHDA rats. First, we tested two doses of CERE-120 ( $0.32 \times 10^9$  &  $1.6 \times 10^9$  vg/hemisphere), each projected to limit NRTN expression to the area in and around the SN ( $1.6 \times 10^9$  vg/hemisphere is

estimated to be the 'human equivalent' dose, based on relative SN volumes in rats, monkeys and humans). CERE-120 was administered unilaterally two weeks prior to ipsilateral 6-OHDA, followed two weeks later by histological assessment. Significant neuroprotection was seen with both CERE-120 SN doses (76% and 81% of intact side, respectively, vs 33% for control;  $p < 0.001$ ). Next, the 'human equivalent' CERE-120 SN dose was combined with the highest striatal dose commonly used in our prior CERE-120 6-OHDA studies ( $4 \times 10^9$  vg), and compared to the striatal dose alone. While both CERE-120 doses/locations protected SN neurons, 'SN plus striatum' was clearly superior to striatum only (88% vs 71%,  $p = 0.01$ ). Finally, we compared the 'human equivalent' CERE-120 SN dose to the  $4 \times 10^9$  vg striatal dose, under conditions when nigrostriatal neurons are undergoing active neurodegeneration. To accomplish this, CERE-120 was administered simultaneously with 6-OHDA and rats euthanized 4 weeks later. When administered to degenerating nigrostriatal neurons, SN-targeted CERE-120 provided ~50% greater neuroprotection than striatal-targeted CERE-120 ( $p < 0.05$ ). Collectively, these data demonstrate that SN-targeted NRTN can provide added protection for nigrostriatal neurons against 6-OHDA and further support the idea of including direct targeting of SN with neurotrophic factors in trials with PD patients.

Disclosures: **A. Wilson**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **C.D. Herzog**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **L. Brown**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **B. Kruegel**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **R.T. Bartus**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest.

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